not hereby abandon or waive any rights in the Group I invention. The restriction requirement is being traversed for the reasons set forth in detail below.

The Examiner alleges that the inventions of Groups I and II, as presently stated in the Office Action, are distinct from each other because the inventions "are not disclosed as capable of use together and they have different modes of operation and different functions" and thus, are unrelated methods. More specifically, the Examiner argues that:

> the method of Invention I operates by training non-human animals and extracting brain-specific RNA for analysis and function to identify non-human gene or genes and the method of Invention II operates by training Drosophila and extracting head tissue-specific RNA for analysis and functions to identify a Drosophila gene or genes.

Applicants respectfully traverse.

The methods defined by Groups I and II are related to each other in that the methods all relate to identifying a gene or genes involved in transcription-dependent memory. In addition, the methods all comprise the steps of (a) training non-human animals under conditions sufficient to induce transcription-dependent memory formation in the animals; and (b) extracting RNA from brain tissue of the trained animals. More specifically, with regard to step (a), the Group II claims require the training of Drosophila. With regard to step (b), the Group II claims require extracting RNA from head tissue of trained Drosophila. Drosophila are non-human animals and Drosophila head tissue is considered to be brain tissue. Thus, the methods defined by Group I include embodiments which are also embraced by the methods defined by Group II. As such, restriction between Groups I and II is improper.

The methods defined by Group I and the methods defined by Group II are also related to each other as a genus and species. M.P.E.P. §§ 806.04 and 809.02. As discussed above, the claims of Group I require in step (a) training non-human animals and in step (b) extracting RNA from brain tissue of the trained animals. The claims of Group II require in step (a) training of Drosophila (which is a non-human animal) and in step (b) extracting RNA from head tissue (which is considered to be brain tissue) of trained Drosophila. Accordingly, Group I is generic to

and embraces Group II. The methods defined in the two groups overlap in the mode of operation and function. As such, restriction is improper.

In addition, Applicants submit that the examination of Groups I and II together would not place an undue burden upon the Examiner. A search of the prior art for the methods defined by one group would also identify prior art that is applicable to the other group. For example, a search of the prior art for the methods defined by Group II would necessarily identify prior art that is applicable to Group I. Thus, no excessive searching burden would be placed upon the Patent Office in examining Groups I and II together.

For the foregoing reasons, reconsideration and withdrawal of the restriction requirement are respectfully requested.

Paragraph 6: Priority

Applicants acknowledge the Examiner's determination that the Provisional Application, filed March 10, 1999, upon which priority is claimed provides adequate support under 35 U.S.C. § 112 for Claims 11-15 and 24-26.

Paragraph 8: Rejection of Claims 11-15 and 24-26 Under 35 U.S.C. § 112, Second Paragraph

Claims 11-15 and 24-26 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Certain claims have been amended in response to the rejection. The amendments are not intended to narrow the scope of the claims. As amended, the claims even more particularly point out and distinctly claim the subject matter which Applicants regard as the invention, thereby obviating this rejection under 35 U.S.C. § 112, second paragraph.

As amended, the indicated claims include the following changes, made in response to the specific rejections made by the Examiner:

a) Claims 11-15 are rejected "as being incomplete in Claim 11 for omitting essential steps, such omission amounting to a gap between the steps". In particular, the Examiner alleges that the omitted steps are "the steps reciting 'conditions appropriate' for training Drosophila to induce

transcription-dependent memory and the steps reciting 'conditions insufficient' for training Drosophila to induce transcription-dependent memory." Applicants respectfully disagree with this assessment.

The test for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification. Orthokinetics, Inc. v. Safety Travel Chairs, Inc., 1 U.S.P.Q.2d 1081, 1088 (Fed. Cir. 1986). If the claims read in light of the specification reasonably appraise those skilled in the art of the scope of the invention, § 112 demands no more. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 231 U.S.P.Q. 81 (Fed. Cir. 1987), *cert. denied*, 480 U.S. 947 (1987).

As defined in the specification, "conditions appropriate" for training Drosophila to induce transcription-dependent memory formation refer to experimental conditions that are used to induce transcription-dependent memory in Drosophila (see, e.g., page 9, lines 11-13). Applicants disclose that transcription-dependent memory formation can be induced in Drosophila using a spaced training protocol (see, e.g., page 6, lines 12-13). Specific examples of spaced training protocols are provided (see, e.g., page 6, lines 12-13; and page 10, lines 7-11). Other experimental conditions that can be used to induce transcription-dependent memory in Drosophila can be determined using art-known methods.

As defined in the specification, "conditions insufficient" for training Drosophila to induce transcription-dependent memory refer to experimental conditions that are used to induce transcription-independent memory but not transcription-dependent memory in Drosophila (see, e.g., page 5, lines 17-19; page 6, lines 9-11; page 9, lines 13-14). Applicants disclose that transcription-independent memory formation can be induced in Drosophila using a massed training protocol (see, e.g., page 6, lines 14-15). Specific examples of massed training protocols are provided (see, e.g., page 6, lines 14-15; and page 10, lines 4-6 of the specification). Other experimental conditions that can be used to induce transcription-independent memory but not transcription-dependent memory in Drosophila can be determined using art-known methods.

Thus, it is respectfully submitted that essential steps are not omitted from Claim 11. Accordingly, one skilled in the art would find Claims 11-15 to be complete and the metes and bounds clear when read in light of the specification.

b) Claims 11-15 are rejected as indefinite in the recitation of "synthesizing DNA probes using the RNA extracted ..." in steps (c) and (f)(iii) of independent Claim 11 because, in the Examiner's assessment "it is unclear how the RNA is used to synthesize the probes."

As suggested by the Examiner, steps (c) and (f)(iii) of Claim 11 have been amended to replace "DNA" with "cDNA" and "using" with "complementary to". Support for the amendment is found in the specification, for example, at page 11, lines 5-6. This amendment is not intended to narrow the scope of the claims.

c) Claims 11-15 are rejected as indefinite in the recitation of "exposing" in step (d) and (f)(iv) of independent Claim 11 because, in the Examiner's assessment, "it is unclear how the DNA probe are exposed". Claims 11-15 are also rejected as indefinite in the recitation of "conditions appropriate for hybridization" in step (d) and (f)(iv) of Claim 11 because "'hybridization' lacks proper antecedent basis in the step of 'exposing'".

As suggested by the Examiner, steps (d) and (f)(iv) of Claim 11 have been amended to replace "exposing" with "hybridizing". This amendment is not intended to narrow the scope of the claims.

d) Claims 11-15 are rejected as indefinite in the recitation "wherein a signal is produced" in steps (d) and (f)(iv) of Claim 11 because, in the Examiner's assessment, "'signal' lacks proper antecedent basis in the probe of (c) and (f)(iii)".

As suggested by the Examiner, steps (c) and (f)(iii) of Claim 11 have been amended to recite "labeled cDNA probes" and steps (c) and (f)(iv) have been amended to insert "from said labeled probe" immediately after "produced". This amendment is not intended to narrow the scope of the claims.

e) Claim 14 is rejected "as being incomplete for omitting essential steps, such omission amounting to a gap between the steps." In particular, the Examiner alleges that the omitted steps are "the steps reciting 'conditions sufficient to induce transcription-independent memory but not transcription-dependent memory'". Applicants respectfully disagree with this assessment.

As discussed above, Applicants disclose in the specification that "conditions sufficient to induce transcription-independent memory but not transcription-dependent memory" can be induced in Drosophila using a massed training protocol (see, e.g., page 6, lines 14-15). Specific examples of massed training protocols are provided (see, e.g., page 6, lines 14-15; and page 10, lines 4-6 of the specification). Other experimental conditions that can be used to induce transcription-independent memory but not transcription-dependent memory in Drosophila can be determined using art-known methods. Thus, it is respectfully submitted that essential steps are not omitted from Claim 14. Accordingly, one skilled in the art would find Claim 14 to be complete and the metes and bounds clear when read in light of the specification.

f) Claims 24-26 are rejected "as being incomplete in Claim 24 for omitting essential steps, such omission amounting to a gap between the steps". In particular, the Examiner alleges that the omitted steps are "the steps reciting 'conditions appropriate' for training Drosophila to induce transcription-dependent'" memory. Applicants respectfully disagree with this assessment.

As discussed above, "conditions appropriate" for training Drosophila to induce transcription-dependent memory refer to experimental conditions that are used to induce transcription-dependent memory in Drosophila (see, e.g., page 9, lines 11-13). Applicants disclose that transcription-dependent memory formation can be induced in Drosophila using a spaced training protocol (see, e.g., page 6, lines 12-13). Specific examples of spaced training protocols are provided (see, e.g., page 6, lines 12-13; and page 10, lines 7-11). Other experimental conditions that can be used to induce transcription-dependent memory in Drosophila can be determined using art-known methods. Thus, it is respectfully submitted that essential steps are not omitted from Claim 24. Accordingly, one skilled in the art would find Claims 24-26 to be complete and the metes and bounds clear when read in light of the specification.

g) Claims 24-26 are rejected as indefinite in the recitation "synthesizing DNA probes using the RNA extracted ..." in steps (c) and (f)(iii) of independent Claim 24 because, in the Examiner's assessment, "it is unclear how the RNA is used to synthesize the probes." It is noted that the

phrase "synthesizing DNA probes using the RNA extracted ..." is recited in steps (c) and (f)(ii), and not in step (f)(iii), of Claim 24.

As suggested by the Examiner, steps (c) and (f)(ii) of Claim 24 have been amended to replace "DNA" with "cDNA" and "using" with "complementary to". Support for the amendment is found in the specification, for example, at page 11, lines 5-6. This amendment is not intended to narrow the scope of the claims.

h) Claims 24-26 are rejected as indefinite in the recitation of "exposing" in independent Claim 24, steps (d) and (f)(iv), because, in the Examiner's assessment, "it is unclear how the DNA probe are exposed". Claims 24-26 are also rejected as indefinite in the recitation of "conditions appropriate for hybridization" in Claim 24, steps (d) and (f)(iv), because, in the Examiner's assessment, "it is unclear what 'conditions are being claimed" and "whether hybridization occurs." It is noted that Claim 24 does not include a step (f)(iv). The terms "exposing" and "conditions appropriate for hybridization" are recited in steps (d) and (f)(iii) of Claim 24.

As suggested by the Examiner, Claim 24 has been amended to replace "exposing" with "hybridizing" and to delete "under conditions appropriate for hybridization to the DNA probes to complementary DNA sequences on the microarray chips". This amendment is not intended to narrow the scope of the claims.

i) Claims 24-26 are rejected as indefinite in the recitation of "wherein a signal is produced" in steps (d) and (f)(iv) of independent Claim 24 because, in the Examiner's assessment, "'signal' lacks proper antecedent basis in the probe of (c) and (f)(iii)". It is noted that Claim 24 does not include a step (f)(iv). The phrase "wherein a signal is produced" is recited in steps (d) and (f)(iii) of Claim 24.

As suggested by the Examiner, steps (c) and (f)(ii) of Claim 24 have been amended to recite "labeled cDNA probes" and steps (d) and (f)(iii) have been amended to insert "from said labeled probe" immediately after "produced". This amendment is not intended to narrow the scope of the claims.

Paragraph 10: Rejection of Claims 11-15 and 24-26 Under 35 U.S.C. § 103(a)

Claims 11-15 and 24-26 have been rejected under 35 U.S.C. § 103(a) as being obvious over Yin *et al.* (*Cell*, 79:49-58 (1994)) in view of Tully *et al.* (U.S. Patent No. 5,929,223) and Luo *et al.* (Society for Neuroscience Abstracts, 25(1-2):2164 (1999)).

Teachings of the Cited References

Yin *et al.*

Yin *et al.* teach the use of a dominant negative CREB transgene to investigate the role of CREB in long term memory (LTM) formation in Drosophila. In particular, Yin *et al.* teach the use of the inducible transgene approach in combination with training protocols for inducing memory formation to investigate the effect of inducing a dominant negative CREB transgene on LTM formation. More specifically, Yin *et al.* teach the production of transgenic flies that express *dCREB2-b* under the control of a heat-shock promoter (*hs-dCREB2-b* transgene), training the transgenic flies which had been heat-shock induced or left uninduced, under conditions appropriate to induce memory formation in the flies, extracting RNA from the head tissue of trained flies, exposing the extracted RNA to a dCREB2-b cDNA fragment under conditions appropriate for hybridization of dCREB2-b transgene RNA to the dCREB2-b cDNA fragment and detecting hybridization of dCREB2-b transgene RNA to the dCREB2-b cDNA fragment. The hybridization signal detected using RNA extracted from the heads of trained transgenic flies is compared to the hybridization signal detected using RNA extracted from the heads of wildtype flies (i.e., flies that do not include the *hs-dCREB2-b* transgene) trained in the same manner as the transgenic flies (Yin *et al.*, page 50, Figure 1A).

Yin *et al.* also disclose the results of behavioral experiments in which the performance index of the trained flies is measured (Yin *et al.*, page 51, column 2 to page 53, column 2) and provide methods for statistically analyzing the behavioral data obtained (Yin *et al.*, page 55, column 2, second paragraph from bottom ("Statistical Analyses of Behavioral Data") to page 56, column 2, fourth full paragraph ("Shock Reactivity in rsh;17-2 Files (Table 1)").

Yin *et al.* do not teach or suggest the use of microarray chips in a method to identify genes involved in transcription-dependent memory formation. Yin *et al.* do not teach or suggest the use of a statistical comparison between signal detected from a control microarray chip and signal detected on a microarray chip using cDNA probes synthesized from RNA extracted from head tissue of Drosophila trained under conditions appropriate to induce transcription-dependent memory to identify genes involved in transcription-dependent memory formation.

Tully *et al.*

Tully *et al.* is cited by the Examiner as teaching "the method wherein the hybridization signals from the spaced trained and massed trained Drosophila are compared." In particular, the Examiner contends that in column 25, lines 6-30, Tully *et al.* teach:

> training two groups of Drosophila, one under conditions to induce transcription-dependent memory and a second under condition insufficient to induce transcription-dependent memory, extracting RNA from head tissue of both groups, hybridizing the RNA to DNA sequences from genes of the Drosophila and comparing the hybridization signals between the two groups.

Paper No. 7, at page 8, lines 6-11. Respectfully, it appears that the Examiner may have misunderstood the cited passage. It is noted that Example 2, which includes column 25, lines 6-30, is the same as or similar to the "Experimental Procedures" (pages 55 to 57) and "Results" (pages 50 to 53) sections of the Yin *et al.* reference.

At column 25, lines 6-30, Tully *et al.* disclose the method for performing Northern analysis, which is the same as or similar to the method disclosed by Yin *et al.* (see Yin *et al.*, at page 56, column 2, last paragraph). At column 26, lines 9-15, Tully *et al.* report the results revealed by Northern analysis, which are the same as or similar to the results reported by Yin *et al.* (see Yin *et al.*, at page 50, column 2, last paragraph).

Similarly, in Example 2, Tully *et al.* teach the use of a dominant negative CREB transgene to investigate the role of CREB in LTM formation in Drosophila. In particular, Tully *et al.* teach the use of the inducible transgene approach in combination with training protocols for inducing memory formation to investigate the effect of inducing a dominant negative CREB

transgene on LTM formation. More specifically, Tully *et al.* teach the production of transgenic flies that express *dCREB2-b* under the control of a heat-shock promoter (*hs-dCREB2-b* transgene), training the transgenic flies which had been heat-shock induced or left uninduced, under conditions appropriate to induce memory formation in the flies, extracting RNA from the head tissue of trained flies, exposing the extracted RNA to a dCREB2-b cDNA fragment under conditions appropriate for hybridization of dCREB2-b transgene RNA to the dCREB2-b cDNA fragment and detecting hybridization of dCREB2-b transgene RNA to the dCREB2-b cDNA fragment. The hybridization signal detected using RNA extracted from the heads of trained transgenic flies is compared to the hybridization signal detected using RNA extracted from the heads of wildtype flies (i.e., flies that do not include the *hs-dCREB2-b* transgene) trained in the same manner as the transgenic flies (Tully *et al.*, column 3, lines 36-41; and Figure 9A).

In Example 2, Tully *et al.* also disclose the results of behavioral experiments in which the performance index of the trained flies is measured (Tully *et al.*, column 26, line 52 to column 28, line 41) and provide methods for statistically analyzing the behavioral data obtained (Tully *et al.*, column 23, line 1 to column 25, line 5).

Tully *et al.* do not teach or suggest the use of microarray chips in a method to identify genes involved in transcription-dependent memory formation. Tully *et al.* do not teach or suggest the use of a statistical comparison between signal detected from a control microarray chip and signal detected on a microarray chip using cDNA probes synthesized from RNA extracted from head tissue of Drosophila trained under conditions appropriate to induce transcription-dependent memory to identify genes involved in transcription-dependent memory formation.

Luo *et al.*

The Luo *et al.* abstract appears in the Society for Neuroscience Abstracts volume for the Society for Neuroscience 1999 Annual Meeting, held October 23-28, 1999, Miami Beach, Florida. The "1999 Call for Abstracts" indicates that the print version of the Abstracts volume was expected to be mailed in late August 1999 (see 1999 Call for Abstracts, at page 2; copy attached as Exhibit). The subject application has an effective filing date of March 10, 1999, as

noted by the Examiner. Accordingly, the Luo *et al.* abstract is not prior art under 35 U.S.C. §§ 102 or 103.

The Combination of References

A *prima facie* case of obviousness is established only if the teachings of the cited art would have suggested the claimed invention to one of ordinary skill in the art with a reasonable expectation of successfully achieving the claimed results. In re Vaeck, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Both the suggestion and the reasonable expectation of success must be found in the prior art, not in Applicants' disclosure. Id.

As discussed above, the Luo *et al.* reference is not prior art under 35 U.S.C. § 103. As such, reliance on the Luo *et al.* reference in the present rejection is improper.

Neither the Yin *et al.* reference nor the Tully *et al.* patent teaches or suggests the use of microarray chips in a method to identify genes involved in transcription-dependent memory formation. Neither the Yin *et al.* reference nor the Tully *et al.* patent teaches or suggests performing a statistical comparison between signal detected from a control microarray chip and signal detected on a microarray chip using cDNA probes synthesized from RNA extracted from head tissue of Drosophila trained under conditions appropriate to induce transcription-dependent memory to identify genes involved in transcription-dependent memory formation. As such, the Yin *et al.* reference and the Tully *et al.* patent, alone or in combination, would not, and could not, have suggested the claimed invention to one of ordinary skill in the art, at the time the invention was made, with a reasonable expectation of success. Accordingly, Claims 11-15 and 24-26 are not obvious in view of the cited art.

Reconsideration and withdrawal of this rejection of Claims 11-15 and 24-26 under 35 U.S.C. § 103(a) are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (781) 861-6240.

Respectfully submitted,

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Dated: May 21, 2001

MARKED UP VERSION OF AMENDMENTS

Specification Amendments Under 37 C.F.R. § 1.121(b)(1)(iii)

Replace the paragraph at page 37, lines 7 through 9 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

Results for each C/EBP reaction were normalized for RNA amounts against a paired QPCR reaction for [TBPββ] TF2D, a control gene which shows no transcriptional changes in these contexts.

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

11. (Amended) A method of identifying a gene or genes involved in transcription-dependent memory comprising the steps of:

(a) training Drosophila under conditions appropriate to induce transcription-dependent memory formation in said Drosophila;

(b) extracting RNA from head tissue of Drosophila trained in step (a);

(c) synthesizing [DNA] labeled cDNA probes complementary to [using] the RNA extracted in step (b);

(d) [exposing] hybridizing the DNA probes synthesized in step (c) to microarray chips containing DNA sequences from genes of the Drosophila genome under conditions appropriate for hybridization of the DNA probes to complementary DNA sequences on the microarray chips, wherein a signal is produced from said labeled probes upon hybridization of said probes to complementary DNA sequences;

(e) detecting the signal produced in step (d); and

(f) performing a statistical comparison between the signal detected in step (e) and the signal detected in a control for each gene, wherein said control is obtained according to a method comprising the steps of:

(i) training control Drosophila under appropriate conditions, wherein said conditions are insufficient to induce transcription-dependent memory formation in said control Drosophila;

(ii) extracting RNA from head tissue of said control Drosophila trained in step (f)(i);

(iii) synthesizing [DNA] labeled cDNA probes complementary to [using] the RNA extracted in step (f)(ii); and

(iv) [exposing] hybridizing the DNA probes synthesized in step (f)(iii) to microarray chips containing DNA sequences from genes of the Drosophila genome under conditions appropriate for hybridization of the DNA probes to complementary DNA sequences on the microarray chips, wherein a signal is produced from said labeled probes upon hybridization of said probes to complementary DNA sequences.

24. (Amended) A method of identifying a gene or genes involved in transcription-dependent memory comprising the steps of:

(a) training Drosophila under conditions appropriate to induce transcription-dependent memory formation in said Drosophila;

(b) extracting RNA from head tissue of Drosophila trained in step (a);

(c) synthesizing labeled cDNA [DNA] probes complementary to [using] the RNA extracted in step (b);

(d) [exposing] hybridizing the DNA probes synthesized in step (c) to microarray chips containing DNA sequences from genes of the Drosophila genome [under conditions appropriate for hybridization of the DNA probes to complementary DNA sequences on the microarray chips], wherein a signal is produced from said labeled probes upon hybridization of said probes to complementary DNA sequences;

(e) detecting the signal produced in step (d); and

(f) performing a statistical comparison between the signal detected in step (e) and the signal detected in a control for each gene, wherein said control is obtained according to a method comprising the steps of:

(i) extracting RNA from head tissue of control Drosophila;

(ii) synthesizing labeled cDNA [DNA] probes complementary to [using] the RNA extracted in step (f)(i); and

(iii) [exposing] hybridizing the DNA probes synthesized in step (f)(ii) to microarray chips containing DNA sequences from genes of the Drosophila genome [under conditions appropriate for hybridization of the DNA probes to complementary DNA sequences on the microarray chips], wherein a signal is produced from said probes upon hybridization of said probes to complementary DNA sequences.